TCA cycle intermediates and particular amino acids that support rapid growth rates of *Pseudomonas*.

3) The *avrB-Rpg1* interaction. Our studies reveal that the HR-inducing ability of *Psg*0 has a rapid turnover time (approximately 10 min). Since it is unlikely that *Psg*0 induces the *Rpg1* gene and then interacts with its product (or with the product of a pathway downstream from the *Rpg1* gene product) within 10 min, the *Rpg1* gene product and the mechanism for *avrB*-specific recognition probably exist in the plant before infection.

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The RNA Processing Enzyme RNase MRP Is Identical to the Th RNP and Related to RNase P

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Sera from patients with autoimmune diseases often contain antibodies that bind ribonucleoproteins (RNPs). Sera from 30 such patients were found to immunoprecipitate ribonuclease P (RNase P), an RNP enzyme required to process the 5′ termini of transfer RNA transcripts in nuclei and mitochondria of eukaryotic cells. All 30 sera also immunoprecipitated the nucleolar Th RNP, indicating that the two RNPs are structurally related. Nucleotide sequence analysis of the Th RNP revealed it was identical to the RNA component of the mitochondrial RNA processing enzyme known as RNase MRP. Antibodies that immunoprecipitated the Th RNP selectively depleted murine and human cell extracts of RNase MRP activity, indicating that the Th and RNase MRP RNPs are identical. Since RNase P and RNase MRP are not associated with each other during biochemical purification, we suggest that these two RNA processing enzymes share a common autoantigenic polypeptide.

PATIENTS WITH SYSTEMIC AUTOIMMUNE diseases, such as systemic lupus erythematosus (SLE), make autoantibodies, which are directed against a variety of intracellular structures. The most common targets of these autoantibodies are ribonucleoproteins (RNPs) and components of chromatin (*1*). Although the precise mechanisms leading to the genesis of autoantibodies are not known, they have served as useful probes to elucidate the structure and function of their intracellular targets. For example, autoantibodies directed against the polypeptide components of the U1 RNP and the related U-series RNPs were crucial tools in the elucidation of the structure of these molecules and their role in the splicing of pre–messenger RNA (*2*).

Sera from certain patients with systemic autoimmune diseases have recently been shown to contain antibodies to ribonuclease P (RNase P) from HeLa cells (*3*). RNase P, one of the best characterized RNA processing enzymes, is an endoribonuclease that processes all precursor tRNA transcripts to generate their mature 5′ termini (*4*). Studies of RNase P from prokaryotic sources have demonstrated that the enzyme has a catalytic RNA and a protein subunit (thus, an RNP) (*5*).

Sera that contain antibodies to RNase P from HeLa cells were found to immunoprecipitate an RNA of ~400 nucleotides from crude cell extracts and from extracts of partially purified RNase P (*3*). This RNA (called H1 RNA) is the only RNA that copurifies with RNase P activity, strongly suggesting that H1 RNA is the RNA component of RNase P (*6*). In addition, the majority of these autoimmune sera immunoprecipitated a second, smaller RNA species of approximately ~300 nucleotides named Th RNA [after the patient whose serum first immunoprecipitated it from cell extracts (*7*)]. Subsequent studies with this prototype serum and with a second serum of the same specificity demonstrated that the Th RNA was bound to at least one unidentified autoantigenic polypeptide (the RNA itself was not antigenic) and was identical to a previously described nucleolar 7-2 RNA (*8*). Indirect immunofluorescence and electron microscopy studies have confirmed the nucleolar location of the Th RNP with the antigenic polypeptide or polypeptides located in the granular region (*8, 9*).

We have now identified 30 patients with autoimmune diseases whose sera immunoprecipitate the Th RNA from crude cell extracts labeled in vivo with [^{32}P]orthophosphate. Serum samples from nine of these patients, including the prototype Th serum, have been described previously (*3, 7, 8*). All 30 sera also immunoprecipitated the H1 RNA of RNase P; representative samples are shown in Fig. 1. Twenty-five of these sera only immunoprecipitated the Th and H1 RNAs (for examples, see lanes 8 to 15 of Fig. 1), while the remaining five contained additional specificities (see lanes 7 and 16). When extracts were deproteinized with phenol or proteinase K, no RNAs were immunoprecipitated. These data strongly suggest that these two RNAs share one or more polypeptides or are physically associated.

The relationship between the RNase P and Th RNPs was examined more closely by sequencing the immunoprecipitated Th RNA. Th RNA is ~80% homologous with the RNA component of mouse mitochondrial RNA processing enzyme (RNase MRP) (*10*) and identical to the RNA component of human RNase MRP (*11*) (Fig. 2).

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RNase MRP makes an endoribonucleolytic cleavage in mitochondrial primer RNA that is believed to be involved in the replication of mitochondrial DNA. The sequence identity between Th RNA and RNase MRP RNA indicates that the Th RNA is the RNA component of RNase MRP. To confirm that the Th RNP is RNase MRP, antibodies that immunoprecipitated the Th RNP from crude cell extracts were used in immunoprecipitation experiments. These antibodies selectively depleted RNase MRP enzyme from mitochondrial extracts of human cells (Fig. 3). Similarly, these antibodies also inhibited RNase MRP activity from nuclear extracts of human cells and mitochondrial and nuclear extracts of mouse cells. Since the immunoprecipitates contain Th RNA (*12*), these experiments demonstrate that Th RNA is the RNA component of RNase MRP.

The inhibition of RNase MRP enzymatic activity by antibodies that immunoprecipitate Th RNP supports the idea that these two RNPs are identical and suggests that the mitochondrial RNP bears the autoantigenic polypeptide found in the nucleolus. Antibodies that immunoprecipitated Th RNA and inhibit RNase MRP enzymatic activity did not stain mitochondria in indirect immunofluorescence (*13*); however, the antigenic polypeptide in mitochondria may be inaccessible to antibodies, present in insufficient copy number, or perhaps altered by cell fixation techniques that prevent it from being detected in this assay. Similar factors may also explain why we have previously noted in indirect immunofluorescence experiments that autoantibodies that inhibit processing of HeLa RNase P do not clearly stain human cell nuclei, where this enzyme resides.

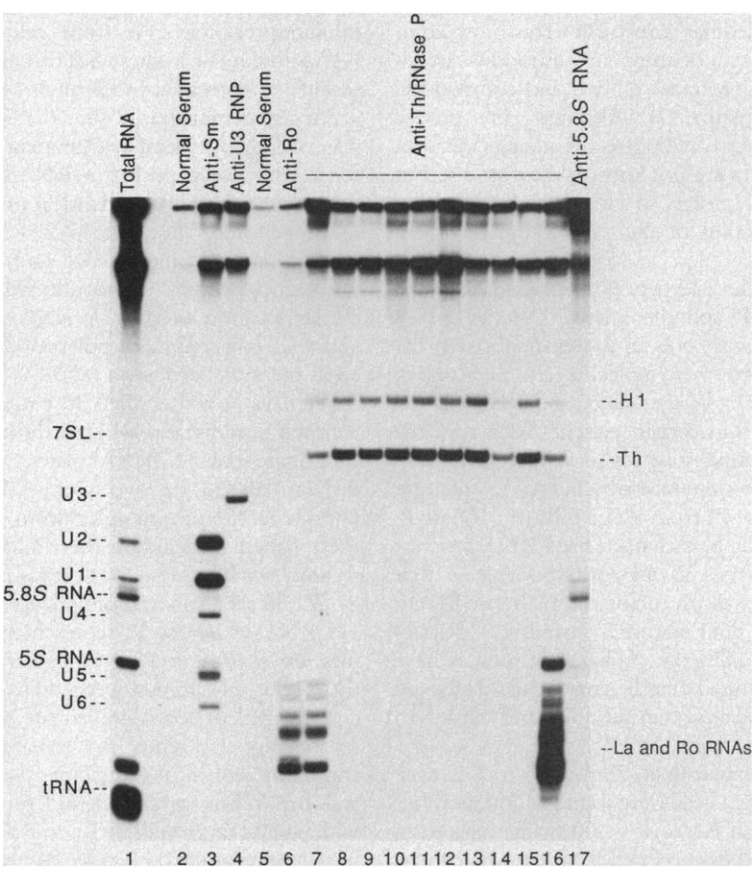

Fig. 1. Immunoprecipitation of Th and RNase P RNPs with sera from patients with autoimmune diseases. Cell extracts labeled with [^{32}P]orthophosphate were prepared and immunoprecipitations were carried out as previously described (*17*). After washing the immunoprecipitates, bound RNAs were extracted, precipitated, fractionated on 5% polyacrylamide and 7*M* urea gels, and detected by autoradiography. Precipitates were obtained with sera from normal volunteers (lanes 2 and 5); from patients with anti-Sm (lane 3), anti-U3 RNP (lane 4), anti-Ro (lane 6), and anti-5.8*S* RNA (lane 17) antibodies; and from ten sera that immunoprecipitated the Th and RNase P RNPs (lanes 7 to 16). Two of the latter sera also had other antibody specificities; anti-Ro (lane 7) and anti-La (lane 16). The serum used in lane 7 is the prototype Th serum. The positions of the Th and H1 RNAs are shown in comparison to other cellular RNAs. DNase treatment of cell extracts removed the upper bands present in all the lanes. Twenty other sera that immunoprecipitated the H1 and Th RNAs were also identified and included three sera with other autoantibody specificities: one serum immunoprecipitated Ro RNAs, one immunoprecipitated U1 and Ro RNAs, and one immunoprecipitated U3 RNA.

Since autoantibodies immunoprecipitate H1 RNA and the Th RNA (RNase MRP RNA) in tandem, their sequences were searched for conserved sequence elements to which a common autoantigenic polypeptide might bind. Such a comparison between HeLa H1 RNA and murine and human RNase MRP RNA shows that, although these RNAs are distinct, they do contain small blocks of conserved sequences, which could serve as a common polypeptide binding site (Fig. 4). Most notable are the conserved sequences in positions 149 to 163 in H1 RNA and positions 242 to 263 in the RNase MRP RNA, where a sequence of nine nucleotides is identical. All four of these conserved sequence elements are found in similar stem structures in both H1 RNA (*6*) and RNase MRP RNA (*11*). Conserved sequence element II exhibits a striking similarity to the site on M1 RNA where C5 protein binds (*14*). When the conserved sequence element II from H1 and RNase MRP RNA is compared with the C5 protein binding site on M1 RNA, a consensus sequence of GGG^{C}_{A} ARG is obtained. The sequences of the corresponding RNAs from other organisms will help determine whether these conserved sequence elements are functionally significant.

Sera that immunoprecipitate H1 and RNase MRP RNAs bring down at least seven polypeptides from HeLa cells labeled in vivo with [^{35}S]methionine (*13*). It will be important to identify the antigenic protein or proteins and determine its binding sites on the RNA components of RNase P and RNase MRP.

The RNA component of mitochondrial RNase MRP is transcribed from a nuclear gene with subsequent transport to the mitochondria, where it functions as an RNP with as yet unidentified polypeptide components that are essential for function (*10*). Although RNase MRP isolated from the nucleus can cleave a mitochondrial RNA substrate, the substrate for the enzyme in the nucleus has not been identified. Since the Th RNP and RNase MRP are the same, it follows that RNase MRP is localized to the granular region of the nucleolus. This region of the nucleolus is the site where pre–ribosomal RNA is processed, and it seems reasonable to propose that RNase MRP is involved in pre–ribosomal RNA processing events.

The co-immunoprecipitation of the RNA component of RNase P (H1 RNA) and the RNA component of RNase MRP (Th RNA) argues that these two site-specific endoribonucleases share some important features such as an antigenic polypeptide. It seems less likely that autoimmune sera that immunoprecipitate both RNAs contain two different antibody specificities, since the

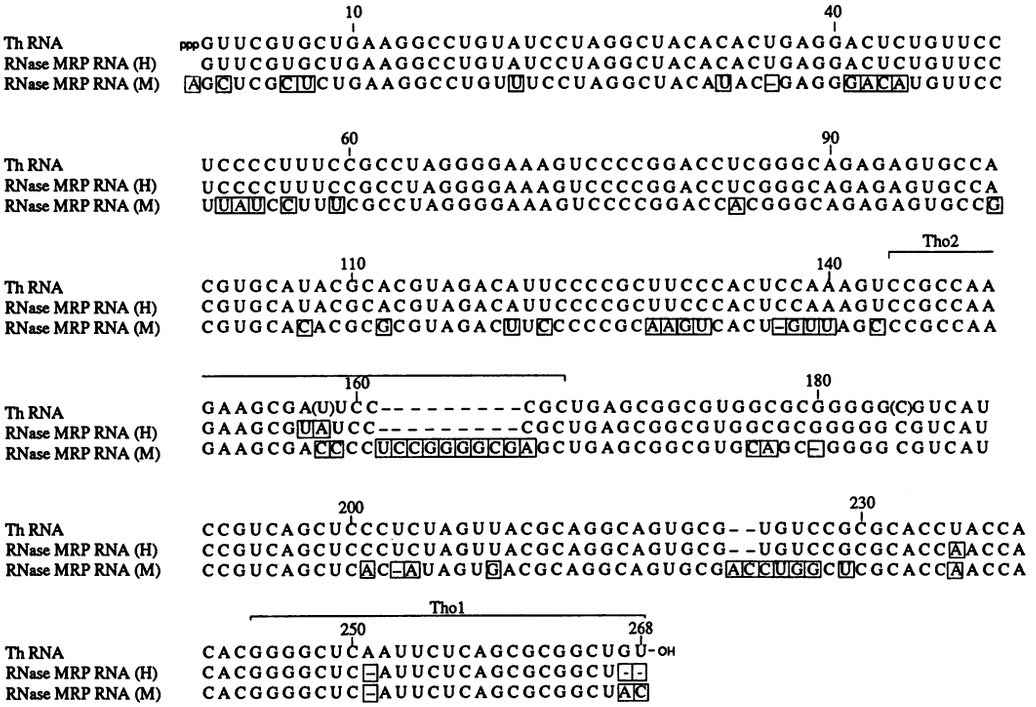

Fig. 2. Sequence comparison of Th RNA and RNase MRP RNA. The sequence of Th RNA is shown on the top line. The immunoprecipitated Th RNA was labeled at its 3′ end with [^{32}P]pCp as described (*18*). The 3′ end nucleotide was determined by digestion with RNase T2 and subsequent electrophoresis on cellulose acetate paper. The 3′ end of the Th RNA was sequenced by the enzymatic cleavage method (*19*) and by wandering spot analysis (*20*). Specific RNases used include RNase T1, RNase U2, RNase Phy M, RNase *Bacillus cereus*, and RNase CL3 from chicken liver. In addition, an RNA sequence ladder was generated by means of alkaline hydrolysis. The sequence of the 3′ end was used to generate a complementary oligonucleotide (Tho1). The 3′ half of Th RNA was sequenced using Tho1, reverse transcriptase, and dideoxynucleotides as described (*21*). A second complementary oligonucleotide Tho2 was used as a primer with reverse transcriptase and dideoxynucleotides to sequence to the 5′ end of Th RNA. The sequences of the RNA components of RNase MRP from human (*11*) and mouse cells (*10*) are shown on the second and third lines, respectively. All nucleotides that are different from those in Th RNA are shown in boxes. Ambiguous nucleotides in the Th sequence are indicated by parentheses. The absence of a nucleotide at that position in the sequence is indicated by a dash. The GU at the 3′ terminus of Th RNA was not detected at the end of RNase MRP RNA by S1 protection experiments (*11*), although these are the next two nucleotides in the genomic sequence. The differences (four nucleotides) between the sequence of the Th RNA and the human RNase MRP RNA are most likely due to ambiguities in RNA sequencing or polymorphisms in the genes for the RNA from human placenta (RNase MRP RNA) and from HeLa cells (Th RNA).

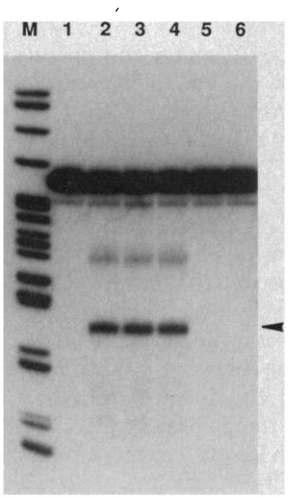

Fig. 3. Immunoprecipitation of RNase MRP activity. Antibodies were coupled to protein A–Sepharose, and depletion experiments were as described (*3*). The assay for RNase MRP activity was done with murine mitochondrial 270-nucleotide RNA substrate and RNase MRP isolated from human mitochondria purified through the glycerol gradient step as described (*10, 11*). Position of the cleavage product is indicated by an arrow. (Lane M) Hpa II fragments of pBR322; (lane 1) substrate alone; (lane 2) mock immunoprecipitation of RNase MRP (no antibodies were coupled to the protein A–Sepharose); (lane 3) immunoprecipitation with a normal human serum; (lane 4) immunoprecipitation with an anti-Ro serum; (lanes 5 and 6) two patients' sera that immunoprecipitated the Th and RNase P RNPs coupled to protein A–Sepharose.

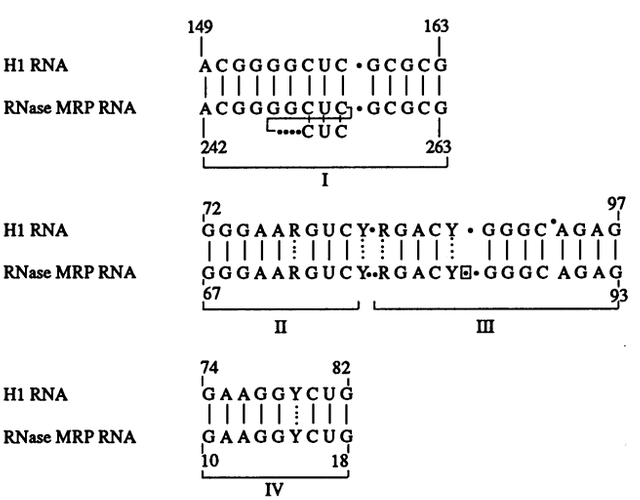

Fig. 4. A sequence comparison of H1 RNA with RNase MRP RNA (Th RNA). The RNA sequences from H1 RNA (from HeLa cells) and RNase MRP RNA (from mouse and human cells) were searched for conserved sequence elements that contained at least eight of nine identical nucleotides. The alignment of conserved nucleotide sequences in these RNAs are shown. An R indicates a purine and a Y indicates a pyrimidine at that position. Purine-to-pyrimidine substitutions and nucleotide insertions are indicated by a · and ⊡ indicates a change in this position in the murine sequence. The first and last nucleotide of the conserved sequence elements are numbered to indicate their corresponding nucleotide positions in the respective RNAs.

known sets of linked autoantibodies do not exhibit this degree of co-occurrence (*1*). It is likely that RNase P and RNase MRP share a common autoantigenic polypeptide, rather than being physically associated, since these enzymes do not copurify by classical biochemical methods. During the purification of HeLa RNase P, only H1 RNA and not Th RNA copurifies with RNase P enzymatic activity (*6*). Similarly, only Th RNA copurifies with RNase MRP enzymatic activity (*10*). In addition, both enzymes can be immunoprecipitated separately from partially purified enzyme extracts (Fig. 4) (*3*), demonstrating that each enzyme contains the antigenic epitope.

RNase P and RNase MRP share several features, some of which may be explained by a common polypeptide. The enzymes have some similar biochemical properties; that is,

both are RNPs, both bind to anion-exchange columns (although they elute at different ionic strengths), and both sediment as a 15*S* particle in glycerol gradients (*6, 10*). Furthermore, RNase P and RNase MRP are both RNA processing enzymes that make a single endoribonucleolytic cleavage in their RNA substrates, a function that could be dependent on a common polypeptide. In addition, both H1 RNA and RNase MRP RNA have a site, approximately in the middle, at which cleavage occurs (*6, 10*). Whether a common polypeptide component of RNase P and RNase MRP is responsible for creating a labile phosphodiester bond and possibly cleaving that bond remains to be determined. It will be important to ascertain the function of the full-length versus the cleaved RNA species in each of these enzymes. Several other RNAs may be cleaved and remain functional (*15, 16*).

Both RNase P and RNase MRP are present in the nucleus and mitochondria of mammalian cells and, at least in the case of RNase P, are known to have the same function in both locations. Since RNase MRP is transported to the mitochondria (*10*), it is possible that RNase P is also transported to the mitochondria and that a common protein is responsible for mitochondrial targeting of these enzymes.

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Synergism Between HIV gp120 and gp120-Specific Antibody in Blocking Human T Cell Activation

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The human immunodeficiency virus (HIV) binds to CD4-positive cells through interaction of its envelope glycoprotein (gp120) with the CD4 molecule. CD4 is a prominent immunoregulatory molecule, and chronic exposure to antibody against CD4 (anti-CD4) has been shown to cause immunodeficiency in mice. T cell–dependent in vitro immune responses can also be inhibited by anti-CD4. Experimental findings reported here indicate that CD4-bound gp120 attracts gp120-specific antibodies derived from the blood of HIV-seropositive individuals to form a trimolecular complex with itself and CD4. Thus targeted to CD4, the gp120-specific antibody functions as an antibody to CD4; it cross-links and modulates the CD4 molecules and suppresses the activation of T cells as measured by mobilization of intracellular calcium (Ca_i^{2+}). The synergism between gp120 and anti-gp120 in blocking T cell activation occurs at low concentrations of both components. Neither gp120 nor anti-gp120 inhibits T cell activation by itself in the concentrations tested.

THE CD4 RECEPTOR EXPRESSED ON lymphoid cells is an immunoregulatory molecule through which the immune system regulates its function (*1, 2*). Antibody reactive with CD4 suppresses T cell–dependent immune responses in vitro and in vivo. HIV, thought to be the causative agent of acquired immunodeficiency syndrome (AIDS), is a ligand of CD4; the virus uses CD4 as receptor to facilitate its entry into cells (*3–5*). The possibility has been considered that, through its interaction with CD4, HIV may influence the host's immune response. After ligation with the viral envelope glycoprotein gp120, CD4 can activate or suppress the function of T cells (*6, 7*). CD4 may undergo phosphorylation as a consequence of its ligation with gp120 (*8*).

HIV-induced pathology becomes manifest after the virus engages the immune system. We speculated that the immune system may participate in the pathogenesis of AIDS and play a contributory role in its own destruction. We report experimental evidence to support this speculation. We show that through its interaction with CD4, gp120 may target the CD4 receptor for antibody that the virus has induced in its host. HIV-specific antibodies can thus react indirectly with the CD4 receptor and, like a typical CD4-reactive antibody, may block an early step in the T cell receptor–mediated activation of gp120-laden CD4 lymphocytes.

The basic experiment to demonstrate a synergism between gp120 and immunoglobulin (Ig) isolated from an AIDS patient's serum in blocking T cell activation is shown in Fig. 1. Human peripheral blood T cells enriched for $CD4^+$ cells were treated with an antibody reactive with a monomorphic determinant of the T cell antigen receptor (Ti). This antibody, WT/31, activates T cells to proliferate when immobilized on a solid support (*9*) and can induce them to mobilize intracellular stores of Ca^{2+} when cross-linked with a second antibody, anti-mouse IgG (Fig. 1A). T cells failed to mobilize intracellular calcium when treated, before stimulation with WT/31, with gp120 and the serum IgG fraction from an HIV-seropositive individual (Fig. 1B). Neither treatment with gp120 alone nor treatment with IgG from an HIV patient alone had an inhibitory effect on intracellular Ca^{2+} mobi-

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